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TITLE: Increasing Mammographic Breast Density in Response to  
Hormone Replacement Therapy and Breast Cancer Risk

PRINCIPAL INVESTIGATOR: Jennifer A. Harvey, M.D.  
Richard J. Santen, M.D.  
Gina R. Petroni, Ph.D.  
Viktor E. Bovberg, Ph.D.  
Mark B. Williams, Ph.D.

CONTRACTING ORGANIZATION: University of Virginia  
Charlottesville, Virginia 22904

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6. AUTHOR(S) :

Jennifer A. Harvey, M.D., Richard J. Santen, M.D., Gina R. Petroni, Ph.D., Viktor E. Bovberg, Ph.D., Mark B. Williams, Ph.d.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Virginia  
Charlottesville, Virginia 22904

E-Mail: jah7w@virginia.edu

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Hormone replacement therapy (HRT) use is associated with a small increased risk of developing breast cancer. Currently, it is not possible to predict which women using HRT are at increased risk of developing breast cancer. HRT causes an increase in mammographic density in 17-73% of women. Women with increased mammographic density are also known to be at increased risk for developing breast cancer. We therefore hypothesize that women who have an increase in mammographic density in response to HRT are at higher risk for developing breast cancer than those women who do not have a change in density in response to HRT. The purpose of this case-control study is to determine if an increase in mammographic density in response to HRT is associated with an increased risk of breast cancer. Breast cancer cases at our institution between 1990-2000 will be evaluated, identifying postmenopausal women using HRT at the time of diagnosis. These women will be matched (1:2, case: control) by age and year of mammogram. Clinical data will be collected. Change in breast density over time will be assessed using quantitative digital analysis. Odds ratios will estimate the association between HRT-associated increase in breast density and risk of breast cancer.

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## **INTRODUCTION:**

Hormone replacement therapy (HRT) slows bone loss and improves quality of life for many women, but its use is also associated with a small increased risk of developing breast cancer (1-3). The estrogen plus progesterone arm of the Women's Health Initiative recently closed due to the increased risk of breast cancer without a benefit in prevention of cardiovascular disease or stroke (4). Many women will still choose to use HRT to treat hot flashes and to improve perceived quality of life despite the small increase in breast cancer risk. Currently, it is not possible to predict which women using HRT are at increased risk of developing breast cancer. On the mammogram, HRT is known to slow the normal involution of the breast and causes an increase in mammographic density in 17-73% of women (Figure 1) (5-8). This effect is more common with use of estrogen with progestin compared to estrogen alone (7). Women with increased mammographic density are also known to be at increased risk for developing breast cancer (9). We therefore hypothesize that women who have an increase in mammographic density in response to HRT are at higher risk for developing breast cancer than those women who do not have a change in mammographic appearance in response to HRT.

The purpose of the work funded by this grant is to determine if an increase in mammographic breast density in response to HRT is associated with an increased risk of breast cancer.

The overall goals of the project, as stated in the original application, are to:

- 1) Determine the association between HRT-induced changes in breast density and incident breast cancer
- 2) Quantify the association between initiation and duration of HRT and subsequent change in breast density
- 3) Demonstrate the utility of digital quantitative techniques for determining and reporting breast density

## **BODY:**

As taken from the original Statement of Work, the tasks scheduled to begin and/ or be completed during the project period are as follows:

### Task 1. Identify potential cases (months 1 –6).

- List of 1340 women diagnosed with breast cancer at the University of Virginia between 1990 and 1999.
- Update patient listing of women with diagnosis of breast cancer at the University of Virginia (UVA) to include those diagnosed in 2000.
- Include: Postmenopausal by natural menopause or hysterectomy with bilateral oophorectomy, and using estrogen and progestin for at least one year.

- Exclude: Premenopausal or perimenopausal, history of hysterectomy without bilateral oophorectomy, HRT use prior to onset of natural menopause, use of estrogen alone, concurrent use of testosterone, women with implants, diagnosis of cancer prior to the index year.

Task 2. Identify potential controls (months 1 – 6).

- Use mammography database and radiology information system to identify controls
- Controls selected using same inclusion/exclusion criteria as cases.
- Controls will be frequency matched to cases in a 2 control: 1 case ratio by year of diagnosis, age ( $\pm 5$  years), and time between pre- and post-HRT mammograms ( $\pm 6$  months).

Task 3. Collect demographic and clinical data (months 7 – 12).

- Use medical records to obtain demographic data
- Collect age, time since menopause, duration of HRT use, parity, age at first childbirth, and height and weight to calculate Body Mass Index (BMI).

Task 4. Locate and select mammograms (months 7 – 12).

- Exclude women with mammograms from other institutions
- Anticipate locating films for approximately 122 cases
- Select pre-HRT mammogram (within one year prior to using HRT)
- Select post-HRT mammogram at least one year after onset of HRT use. Closest date will be used (within 5 years after onset of HRT use).

Task 5. Determine pre-HRT breast density, and the change in breast density with HRT use using digital assessment (months 13 - 18).

- Digitize pre- and post-HRT mammograms.
- Assess breast density of pre- and post-HRT mammograms using digital quantitative analysis to obtain the percentage of the breast occupied by breast tissue.
- Obtain the change in breast density by:

$$\begin{array}{l} \text{\% breast occupied} \\ \text{by breast tissue}_{\text{post-HRT}} \end{array} - \begin{array}{l} \text{\% breast occupied} \\ \text{by breast tissue}_{\text{pre-HRT}} \end{array} = \text{change in density}$$

Task 6. Analyze data and perform statistical analysis (months 19 – 24).

- Summarize patient characteristics for cases and control groups.
- Determine if these data provide evidence that women undergoing HRT who developed breast cancer are more likely to have an increase in mammographic breast density than those who did not develop breast cancer.

- Estimate the odds ratio and construct a 95% confidence interval around the point estimate with and without adjustment for confounding factors.

## **ACCOMPLISHMENTS:**

In regards to Task 1, we have obtained lists of women diagnosed with breast cancer at UVA between 1991-2000 through our pathology department, via searching for both women who underwent mastectomy or lumpectomy during this time period. These lists are being cross-checked through our mammography biopsy database to ensure completeness of data collection. Our research technologist has reviewed 924 records to date, which represents about two-thirds of the records to be reviewed. The majority of cases reviewed have been between 1991-1997. Of the reviewed cases, 695 women have been excluded due to premenopausal or perimenopausal status, having no mammograms prior to cancer diagnosis at UVA, implants or other criteria as listed in Task 1. To date, we have identified 107 postmenopausal women using HRT at the time of cancer diagnosis. Of these, 42 used estrogen and progesterone. We anticipate accessing a greater number of useable cases as we complete evaluation of patients between 1997-2000 since HRT use increased in popularity during this time. If an inadequate number of cases of women using estrogen + progesterone are acquired, we will use all cases of HRT use.

In order to perform more appropriate matching, we have elected to delay control selection (Task 2) until cases are obtained.

Clinical and demographic data, except height and weight, have been collected on all cases to date as this has been done at the time of case ascertainment (Task 3). We will continue to obtain this information as additional cases are accrued.

We have already excluded women that do not have prior mammograms at UVA (Task 4), reducing the likelihood that the number of HRT users will be significantly further reduced. We have centralized patient film jackets of the HRT users to ease mammogram selection (Task 4). We have started scanning cases (about 18 to date) in preparation for digital density assessment.

Tasks 5 and 6 will be accomplished during the second year of funding as stated in the original proposal. Prior to assessing the mammograms for a change in breast density for study cases and controls (Task 5), it has become apparent that a meaningful change in breast density must be defined. To this end, we selected 28 cases of postmenopausal women reported to have a change in breast density due to HRT use in 1997-1998. Ten control cases of postmenopausal women with no change in density during the same time period were selected. Mammograms were digitized using a high-resolution Lumisys 75 scanner. Density was visually assessed by one radiologist experienced in breast imaging and classified as 0: No change, +1: Focal or minimal increase in density less than one BIRADS category, +2: Moderate increase in density of one BIRADS category, and +3: Marked increase in density of one or more BIRADS categories with an associated increase in breast size. Digital assessment was performed using segmentation and interactive thresholding to obtain percent density.

**Results:** Visual assessment resulted in assignment of 9 cases in +1, 10 cases in +2, and 9 cases in +3. Digital assessment of breast density resulted in a mean increase of 6.8% in the +1 group (range 2.0-13.8%), 18.7% in the +2 group (range 13.4-25.2%), and 37.4% in the +3 group (range 25.5-46.6%). The control group had a mean decrease of 1.4% (range +2.3 to -3.5%).

**Discussion:** Previous studies assessing a change in breast density have used a visual assessment or changes in BI-RADS or Wolfe's categories. Those using visual assessment have not defined the degree of change, which may lead to variability between readers and studies. Use of change in BI-RADS or Wolfe's categories over time is more quantitative, but is a rather coarse assessment of change. In this study, we have defined changes in breast density in clinically meaningful categories and have correlated these with digital assessment of percent change in density. Changes in mammographic density may signify changes in breast cancer risk. These definitions may be useful for quantifying the percentage of women with minimal, moderate, and marked changes in breast density due to different stimulatory or preventive hormonal regimens.

\*This abstract to be presented in poster format at the 25<sup>th</sup> Annual San Antonio Breast Cancer Symposium, December 11-14, 2002, San Antonio, Texas.

The above results will be used in our study analysis, by defining a significant change in breast density as >5%.

#### **KEY RESEARCH ACCOMPLISHMENTS:**

- Reviewed 972 records (about two-thirds of breast cancer cases available for review), obtaining 107 cases of women using HRT (42 women using estrogen and progesterone).
- Women without prior mammograms at UVA have already been excluded decreasing the likelihood of further case exclusions.
- Clinical data (except height and weight) has been obtained on all collected cases to date.
- Established a scale of clinically meaningful change in breast density for women using HRT by visual and digital assessment techniques.

#### **REPORTABLE OUTCOMES:**

##### *Scientific Presentations:*

Harvey JA, Williams MB, Petroni G, Bovberg V. Increasing Mammographic Breast Density in Response to Hormone Replacement Therapy and Breast Cancer Risk. The

Department of Defense Breast Cancer Research Program Meeting: Era of Hope,  
September 25-28, 2002, Orlando, Florida.

Harvey JA, Williams MB, Petroni G, Bovberg V. Establishing a Scale of Clinically Meaningful Change in Breast Density in Women using Hormone Replacement Therapy Using Visual and Digital Assessment Techniques. 25<sup>th</sup> Annual San Antonio Breast Cancer Symposium, December 11-14, 2002, San Antonio, Texas.

## CONCLUSIONS:

We have reviewed about two-thirds of the breast cancer cases available at UVA and obtained a reasonable number of cases of postmenopausal women using HRT at the time of cancer diagnosis. We anticipate obtaining more cases as we complete our chart reviews as HRT use became more popular in the late 1990s. The cases accrued are already known to have prior mammograms at our institution. In order to perform the density assessment, we developed a scale of meaningful change in breast density for women using HRT. This will aid in our data analysis.

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**APPENDICES:**

None